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Remarks

Claims 44-68 remain pending after entry of this amendment. Claims 44, 54, 56, and 57 were amended herein. Claims 66-68 were added herein. Favorable reconsideration is respectfully requested in light of the amendments and remarks submitted herein.

Restriction

The Examiner asserts that previously presented claim 65 is directed to an invention that is independent or distinct from the invention originally claimed because the originally claimed method is a screen for compounds potentially active in the field of lipolysis, but claim 65 is a method of evaluating the effectiveness of a slimming care or treatment. Applicant respectfully disagrees.

Claim 65 is dependent from claim 44 and is therefore directed to a method of screening compounds potentially active in the field of lipolysis. Claim 65 is a further step of the method of screening compounds of claim 44 (which comprises a step c) of determining the capacity of inhibition of the release of the fatty acid resulting from the activity of the lipoprotein lipase) to evaluate the effectiveness of a slimming treatment or care. Claim 65 therefore corresponds to the same invention as claimed in claims 44 to 64, and Applicant respectfully requests that the Examiner reconsider the placement of claim 65 within the non-elected invention.

Rejection under 35 U.S.C. § 112

Claims 44-64 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for testing in the presence and absence of inhibitor and comparison to a second inhibitor does not reasonably provide enablement for comparison to the absence of a second inhibitor. Applicant respectfully traverses this rejection.

Although Applicant does not necessarily agree with the Examiner, claim 44 has been amended to remove the terms "or a reference" and "and wherein the reference is a capacity of inhibition in the presence of an inhibitor known to be active in the field of lipolysis". Therefore, amended claim 44 mentions that testing is carried out in the presence and in absence of inhibitor. Furthermore, in all relevant claims "fatty acids" has been amended to refer to the singular "fatty acid".

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Applicant does not screen compounds in order to find compounds which could have a better inhibition capacity of LPL, but instead screen compounds to find those that have a capacity of inhibition of LPL. The reference to a known inhibitor acts merely as a security to measure the inhibition capacity of the screened compounds. This can allow the user of the method of screening to ensure that the assay is being carried out correctly because the capacity of inhibition of the known inhibitor acts as a positive reference.

This is a practical advantage to the Applicant's assay, but there is no need to compare the value of capacity of inhibition of LPL to this positive reference. Other methods undertake the comparison by running a control that comprises the same reaction protocol in the absence of the substance potentially active in the field of lipolysis.

Claims 54-55, and 57 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses this rejection.

Claim 54 was amended in the June 16, 2003 response to clarify that step b) of claim 44 comprises three steps (a), b) and c)). Step b) of claim 44 comprises placing a substrate in contact with a substance which is potentially active in the field of lipolysis, with a lipoprotein lipase, in the presence of a cofactor of lipoprotein lipase. Claim 54 recites that this method step is carried out by:

a) incubating the lipoprotein lipase for a determined period of time in the presence of the substance which is potentially active in the field of lipolysis,

b) incubating the substrate in the presence of a lipoprotein lipase cofactor,

c) incubating the mixture of the substrate/lipoprotein lipase cofactor in the presence of the enzyme lipoprotein lipase and the potentially substance active in the field of lipolysis.

Claim 54 was further amended herein to avoid the phrase "as an inhibitor" which the Examiner asserts lacks antecedent basis. The term "an inhibitor" of claim 54 corresponds to the potentially substance active in the field of lipolysis. Applicants amended the term "an inhibitor" in order to recite "the potentially substance active in the field of lipolysis". Claim 54 has also been amended to recite "the substance which is potentially active in the field of lipolysis" instead of "the substance which is potentially active as an inhibitor". In addition, Applicant has deleted the phrase "which comprises the triacylglycerol" in step b) of claim 54. Applicant has also

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amended triacylglycerol of step c) into "substrate" and "as an inhibitor" into "in the field of lipolysis".

Claim 56 has been amended to delete the phrase "or a reference".

Claim 57 has been amended to delete the phrase "or with a reference inhibitor" (x 2), "positive or negative", and "significant or non significant". Applicant also amended claim 57 to replace the phrase "at the wavelength" by "at 550nm" in order to recite clearly the antecedent basis.

Applicant has also added new claims 66, 67, and 68. Claim 66 specifies that the control is the capacity of inhibition obtained in the absence of the potentially active substance and in the presence of an inhibitor known to be active in the field of lipolysis. Claim 67 specifies that the control is the capacity of inhibition obtained in the presence of an inhibitor known to be active in the field of lipolysis. Claim 68 recites the known inhibitors shown in Table 1, page 13 of the specification.

In light of the claim amendments and the remarks offered above, Applicant respectfully asserts that the rejections under 35 U.S.C. § 112 be withdrawn.

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 44-64 under 35 USC § 103 (a) as being unpatentable over Cook et al., Wagle et al., Takahashi et al., Takeda et al., Vainio et al., Cheng et al., Carroll et al. and Bensadoun et al. in view of NEFA-C Kit from Wako in view of NEFA-C Kit instructions and Kikuchi et al. Applicant respectfully traverses this rejection.

Applicant respectfully disagrees with the Examiner's reasoning. The Examiner cannot consider that it was obvious to a skilled person in the art to carry out the present invention in view of the combination of 8 documents in view of NEFA-C Kit from Wako.

The newly cited documents corresponding to Yamada et al. (US 4,229,538) Kikuchi et al. (US 4,301,244), Numa et al. (US 4,304,864) were filed in 1979 (Yamada et al.) or 1980 (Kikuchi et al. and Numa et al.) and published respectively in 1980 and 1981.

It cannot reasonably be considered that it was obvious to combine all cited documents, in particular Vaino et al. (which is considered by Applicants to be the closest prior art document to

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the present invention), with instruction of NEFA-C Kit. This combination has not been done since 1981 (date of publication of Kikuchi et al.).

Indeed, Takahashi et al. was published in 1999, Takeda et al. was published in 1993, Vaino et al. was published in 1982, Cheng et al. was published in 1990, Carroll et al. was published in 1992, Bensadoun et al. was published in 1974, and Cook et al. was published in 1999. Applicant also asserts that because of the timeframe spanned by the publications, one of skill in the art would not have been motivated to combine these references. It is not likely that one of skill in the art would have combined more recent references, such as those from 1999, with references from 1974.

One of skill in the art would not be motivated to combine an enzymatic technique, in particular the NEFA-C Kit, to provide a kinetic assay of the inhibition capacity of potentially active substances upon a reaction medium comprising LPL, apo-C II and BSA, thereby providing evidence of non-obviousness of the invention over the prior art.

The newly cited documents (Numa et al., Kikuchi et al., Yamada et al., and instruction of NEFA-C Kit from Waco) do not provide any motivation or suggestion to combine these references with a method assaying LPL activity, and certainly not to screen compounds. Prior art documents disclosing NEFA-C Kit focus on the assay of free fatty acids content in a serum and do not disclose assaying FFA in a sample containing LPL, a cofactor of LPL, BSA and a substance which is potentially active in the field of lipolysis.

For example, Kikuchi et al. recites in the abstract that it provides a method for quantitative analysis of free fatty acids. There would have been mo motivation from that teaching to provide a method of screening compounds based on their capacity of inhibition of LPL in a reaction medium that mimics *in vivo* solutions and also includes a potentially active substance which could inhibit LPL. The screening method of the invention is used to determine compounds which are active in the field of slimming care or treatment. This is a different goal.

Takeda et al. discloses on columns 3 and 4 the quantitative determination of free fatty acids (FFA) before that of glycerol formed through the action of LPL on lipoprotein for example prepared from olive oil (column 3, lines 52-60).

It results from column 4, lines 3 to 10 that after completion of the reaction, the test tube is soaked to stop the reaction. After cooling of the tube, isopropanol is added to the reaction system

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and then centrifuged in order to obtain a supernatant. The text, column 4, lines 37 to 42 explains that the fatty acid formation activity can be determined by assaying an isopropanol extract obtained in the same manner for the formed fatty acid content by the use of a commercially available kit for determining free fatty acids (NEFA-C Test).

A method of screening compounds based on the capacity of inhibition of LPL is not disclosed in this document.

In addition, one of skill in the art would not have been motivated to modify the teaching of Takeda because Takeda et al. does not disclose the presence of a cofactor of LPL. There is no reasonable expectation of success that NEFA-C Kit will correctly work to evaluate the inhibition effect of any substances screened introduced in the reaction medium comprising LPL, a cofactor of LPL, and BSA in the presence of a triacylglycerol.

Takeda et al. which was published in 1993 (i.e. after of Kikuchi et al. which was published in 1981) suggests to a skilled person in the art to stop the reaction and to extract free fatty acids with isopropanol in order to perform a colorimetric assay to determine FFA content.

Contrary to that, the present invention provides, for the first time, an industrial method of screening a multitude of substances to determine their capacity to inhibit the LPL activity. The inventive method comprising a colorimetric assay directly carried out upon the reaction medium, comprising LPL, or cofactor of LPL, BSA and triacylglycerol. This is clearly different from a method of assaying the FFA content of a sample.

Takeda et al. does not aim to provide a screening method for compounds which inhibit LPL in view of identifying compounds which are active in the field of lipolysis and in particular for slimming treatment or slimming care. The present invention is capable of determining the inhibition capacity of different substances to be tested in order to determine those which could be used as an LPL inhibitor.

Furthermore the method of the present invention is "normed" to achieve an industrial screening. In view of this, the Examiner's remarks about obtaining an approximate continuous monitoring of the extent of reaction by using a series of endpoints, is believed to be irrelevant. Indeed this method has nothing to do with a screening method which must be easy to use and which must quickly determine the capacity of inhibition of the tested substances.

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The present invention provides such a screening method, and Applicant asserts that it was non-obvious to provide the screening method of the present invention in view of Takeda et al. as well as the combination of Takeda with the other cited prior art.

Vaino et al. aims to study the inhibition of LPL by benzene boronic acid. Vaino et al. discloses a method for assaying a medium comprising LPL, a cofactor of LPL (apolipoprotein C-II, by radioactivity. As such, this document does not provide a method of screening compounds to determine their capacity for the inhibition of LPL.

In Vaino et al., there is no indication or suggestion to combine this document with a document disclosing a colorimetric assay like NEFA-C test. It should be noted that Vaino et al. was published in 1982 and that all patents on acyl-CoA synthetase (corresponding to NEFA-C Kit) were published around 1980. From this date, no one of skill in the art was able to provide the combination of these documents and to achieve the screening method of the present invention which was unobvious.

Applicant also respectfully asserts that the remaining references do not remedy the shortcomings of Takeda and Vaino, and that therefore, this rejection should be withdrawn.

Conclusion

In view of the amendments and comments presented herein, favorable reconsideration in the form of a Notice of Allowance is respectfully requested in view of claims 44 to 67.

Respectfully submitted,
MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
612.332.5300

Date:_____

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John J. Gresens
Reg. No. 33,112
JJG/AMN/vh